AMENDMENTS

In the specification:

On page 9, please amend the paragraph containing line 20 as follows:

FIGS. 1A-1C (SEQ ID NO:1)depicts a nucleotide sequence of a human uroplakin II 5' flanking region. Position +1 (the translational start site) is denoted with an asterisk (in Fig. 1A, nucleotide number 1 represents nucleotide -2239; nucleotide number 430 represents nucleotide -1809).

B1

On page 9, please amend the paragraph containing line 24 as follows:

SUB F1

FIGS. 2A-2E (SEQ ID NO:2)depicts a nucleotide sequence of a mouse uroplakin II 5' flanking region. The translational start site is denoted with an asterisk (in Fig. 2A, nucleotide number 1 represents nucleotide -3592).

B2

On page 11, please amend the paragraph containing line 4 as follows:

FIG. 12 provides a nucleic acid and amino acid sequence for ADP (SEQ ID NOs:3 and 4).

B3

On page 24, please amend the paragraph containing line 13 follows:

An "ADP polypeptide" is a polypeptide containing at least a portion, or region, of the amino acid sequence of an ADP (see, for example, SEQ ID NO:4), and which displays a function associated with ADP, particularly cytotoxicity, more particularly, cell lysis. As discussed herein, these functions can be measured using techniques known in the art. It is understood that certain sequence variations may be used, due to, for example, conservative amino acid substitutions, which may provide ADP polypeptides.

B4

On page 46, please amend the paragraph containing line 17 as follows:

In one aspect of the present invention, the adenovirus vectors comprise co-transcribed first and second genes under control of a urothelial cell-specific TRE, such a hUPII TRE, wherein the second gene is under translational control of an internal ribosome entry site (IRES). IRES elements were first discovered in picornavirus mRNAs (Jackson RJ, Howell MT, Kaminski A (1990) *Trends Biochem Sci* 15(12):477-83) and Jackson RJ and Kaminski, A. (1995) *RNA* 1(10):985-1000). The present invention provides improved adenovirus vectors comprising co-transcribed first and second genes under transcriptional control of a heterologous, target cell-specific TRE, and wherein the second gene (i.e., coding region) is under translational control of an internal ribosome entry site (IRES). Any IRES may be used in the adenovirus vectors of the invention, as long as they exhibit requisite function in the vectors. Example of IRES which can be used in the present invention include those provided in Table 6 and referenced in Table 7. Examples of IRES elements include the encephelomycarditis virus (EMCV) which is commercially available from Novagen (Duke et al. (1992) *J. Virol* 66(3):1602-9) the sequence for which is depicted in Table 6 (SEQ ID NO:42). Another example of an IRES element disclosed herein is the VEGF IRES (Huez et al. (1998) *Mol Cell Biol* 18(11):6178-90). This IRES has short segment and the sequence is depicted in Table 6 (SEQ ID NO:43).

On page 75, please amend the paragraph containing line 12 as follows:

Accordingly, the invention provides an adenoviral vector that includes a polynucleotide sequence encoding an ADP. A DNA sequence encoding an ADP and the amino acid sequence of an ADP are depicted in SEQ ID NO:3 and SEQ ID NO:4 respectively (Figure 12). Briefly, an ADP coding sequence is obtained preferably from Ad2 (since this is the strain in which ADP has been more fully characterized) using techniques known in the art, such as PCR. Preferably, the Y leader (which is an important sequence for correct expression of late genes) is also obtained and ligated to the ADP coding sequence. The ADP coding sequence (with or without the Y leader) can then be introduced into the adenoviral genome, for example, in the E3 region (where the ADP coding sequence will be driven by the MLP or the E3 promoter). The ADP coding sequence could also be inserted in other locations of the adenovirus genome, such as the E4 region. The ADP coding sequence could also be operably linked to any of the urothelial-cell specific TREs described herein.

On page 99, please amend the paragraph containing line 10 as follows:

A 3.6 kb portion of 5'-flanking DNA a mouse UPII was amplified from mouse genomic DNA using PCR with primers 66.119.1 and 66.119.2.

B7

66.119.1 (5'-ACCGGTCTCGAGGATCTCGGCCCTCTTTC-3', SEQ ID NO:5)

66.119.2 (5'-ACCGGTACTGCGCTGGGACTGGATCC-3', SEQ ID NO:6)

On page 99, please amend the paragraph containing line 16 as follows:

B8

The amplified fragment was purified, then "TA" cloned by ligation into pGEM-T (Promega) to created plasmid CN568. The entire insert was amplified from CN568 with primers 100.24.1 (5'-AAGCTTACCGGTACTGCGCTGGGACTGGATCCTG-3', SEQ ID NO:7) and 100.27.1 (5'-ACCATGGACCGGTCTCGAGGATCTCGGCCCTCTTTC-3', SEQ ID NO:8), purified, and ligated into pGEM-T to create plasmid CP616. CP616 was digested with HindIII and SpeI, blunted and ligated into pGL3-Basic (Promega) which had been digested with HindIII and MluI and blunted, creating plasmid CP620. CP620 contains the 3.6 kb mUPII 5'-flanking DNA (nucleotides -3531 to +60) in operable linkage with the *luc*+ gene.

Beginning on page 99, please amend the paragraph containing line 27, and continuing on page 100 please amend the paragraph containing line 2 as follows:

B9

Plasmids CP619 and CP618 were created with a similar strategy. A 1.0 kb fragment (-965 to +1) of the 5' flanking DNA from the mUPII gene with primers 100.24.1 and 100.24.3 (5'-ACCATGGACCGGTACGTACCCAATCTGTTGTCCCAG-3', SEQ ID NO:9) and a 600 bp fragment (-587 to +1) of the 5'-flanking DNA from the mUPII gene was amplified with 100.24.1 and 100.24.2 (5'-ACCATGGACCGGTCACTAGCCTTGCTGGACTGGAC-3', SEQ ID NO:10). Each fragment was purified then TA cloned into pGEM-T, creating CP615 and CP614, respectively. The 1.0 and 0.6 kb fragments were excised from CP615 and CP614 by digestion with SpeI, purified, blunted and digested with HindIII, then ligated into pGL3-Basic (Promega)

which had been digested with MluI, blunted, and digested with HindIII, creating plasmids CP619 and CP618, respectively.

On page 100, please amend the paragraph containing line 13 as follows:

5' flanking DNA from human UPII was isolated from human genomic DNA using a Human GenomeWalker kit from Clontech (Palo Alto, CA) according to the manufacturer's instructions. Briefly, a first PCR reaction was performed using the AP1 primer supplied in the kit in combination with a hUPII-specific 3' primer, 100.84.1, which is complementary to positions +24 to +47 of the hUPII gene (5'-AAGAATCAGGATCAAGGGCAAGTC-3', SEQ ID NO:11). The product of the first PCR reaction was then amplified a second time using a nested set of primers consisting of AP2 (supplied in the kit) and 100.84.2, which is complementary to positions +3 to -22 of the hUPII gene (5'-AATGCTGGGCTGGGAGGTGGAATAG-3', SEQ ID NO:12). Five major amplification products from the second PCR reaction were TA cloned into pGEM-T. One clone, #7, were identified as containing a 2.2 kb segment of DNA from the 5'-flanking region of hUPII. The 2.2 kb segment was subcloned by amplification using primers 100.113.1 (5'-AGGGGTACCCACTATAGGGCACGCGTGGT-3', SEQ ID NO:13) and 100.113.2 (5'-ACCCAAGCTTGGGATGCTGGGCTGGGAGGTGG-3', SEQ ID NO:14), purification, and TA cloning into pGEM-T, creating CP655. The insert was then excised by digestion with HindIII and SpeI, purified and blunted. The 2.2 (-2225 to +1) kb fragment from CP655 was cloned into pGL3-Basic which had been digested with SacII, blunted, and digested with KpnI, creating CP657. A second clone (#16) contained a 1.0 kb fragment of 5'-flanking DNA. This fragment was subcloned by amplification with primers 100.113.1 and 100.113.2, purification, and TA cloning into pGEM-T to generate CP654. The 1.0 kb insert (-965 to +1) was excised from CP654 with KpnI (blunt) then HindIII, and cloned into pGL3-Basic which had been digested with SacII, blunted, and digested with HindIII to create CP656.

On page 101, please amend the paragraph containing line 8 as follows:

Additional, smaller fragments (0.6 kb and 0.2 kb) of the 5'-flanking region from hUPII were amplified from using 100.126.3 (5'-ACGAGGGGTACCCACCGGTACCGCATGTGCTCCCTGGCC-3', SEQ ID NO:15) plus 100.126.1 (5'-AGACCCAAGCTTGGGACCGGTATGCTGGGCTGGGAGGTGG-3', SEQ ID NO:16) and 100.126.2 (5'-ACGAGGGGTACCCACCGGTCCCCCCTCCTGGCCTGAGG-3', SEQ ID NO:17) plus 100.126.1, respectively, purified, and TA cloned into pGEM-T, creating CP658 and CP659, respectively. CP658 and CP659 were each digested with KpnI and HindIII to excise the 0.6 (-592 to +1) and 0.2 (-211 to +1) kb hUPII 5'-flanking fragments, which were each purified and cloned into pGL3-Basic which had also been digested with KpnI and HindIII, creating CP662 and CP663, respectively.

On page 101, please amend the paragraph containing line 20 as follows:

Two segments of 5'-flanking sequence from human UP1a were cloned by amplifying human genomic DNA with primers 100.82.1 (5'-AGGGGTACCCCGGCCGGTCACACAGCAGGAGAGACAC-3', SEQ ID NO:18) plus 100.82.2 (5'-ACCCAAGCTTGGGCGGCCGCATCCTGGGACACATGAGCAGG-3', SEQ ID NO:19) and 100.82.2 plus 100.83.1 (5'-AGGGGTACCCCGGCCGCAACCCTGCCTTCGAGGTTC-3', SEQ ID NO:20), and TA cloning the amplification products into pGEM-T, creating CP646 (1.0 kb fragment) and CP647 (2.0 kb fragment). CP646 and CP647 were each digested with KpnI and HindIII to excise the inserts, which were each purified and cloned into pGL3-Basic which had been KpnI/HindIII digested, creating CP648 and CP649, respectively. The characteristics of the various plasmids are summarized in Table 1 (Fig. 3).

On page 108, please amend the paragraph containing line 9 as follows:

The 519 base pair EMCV IRES segment was PCR amplified from Novagen's pCITE vector by primers A/B:

B13

primer A: 5'-GACGTCGACTAATTCCGGTTATTTTCCA (SEQ ID NO:21)

primer B 5'-GACGTCGACATCGTGTTTTTCAAAGGAA (SEQ ID NO:22) (*GTCGAC* is a SalI site).

On page 109, please amend the paragraph containing line 7 as follows:

CP1088

B14

The 2.2kb (-2225 to +1) human UPII was amplified from CP657 with primer 127.2.1 (5'-AGGACCGGTCACTATAGGGCACGCGTGGT-3' (SEQ ID NO:23)) PLUS 127.2.2 (5'-AGGACCGGTGGGATGCTGGGCTGGGAGGTGG-3' (SEQ ID NO:24)) and digested with PinAI and ligated with CP629 cut with PinAI.

Beginning on page 111, please amend Table 5 as follows:

B15

TABLE 5

Name	Vector	Ad 5 Vector	E1A TRE	E1B TRE	E3
CV874	CP1086	pBHGE3	1.9 kb mUPII	IRES	intact
CV875	CP1087	pBHGE3	1.0 kb hUPII	IRES	intact
CV876	CP1088	pBHGE3	2.2 kb hUPII	IRES	intact
CV877	CP1089	pBHGE3	1.0 kb mUPII	1.0 kb hUPII (E1B promoter deleted)	intact
CV882	CP1129	pBHGE3	1.8 kb hUPII	IRES	intact
CV884	CP1131	pBHGE3	1.8 kb hUPii	IRES (E1B 19-kDa deleted)	intact

Viruses are tested and characterized as described above.

Primer sequences:

96.74.1	GACGTCGACATCGTGTTTTTCAAAGGAA (SEQ ID NO:22)
96.74.2	GACGTCGACTAATTCCGGTTATTTTCCA (SEQ ID NO:21)
96.74.3	CCTGAGACGCCCGACATCACCTGTG (SEQ ID NO:25)
96.74.4	TGCTGAATGGTCGACATGGAGGCTTGGGAG (SEQ ID NO:26)
96.74.5	CACAACCGCTCTCCACAGATGCATG (SEQ ID NO:27)
96.74.6	GTCGACCATTCAGCAAACAAAGGCGTTAAC (SEQ ID NO:28)
100.113.1	AGGGGTACCCACTATAGGGCACGCGTGGT (SEQ ID NO:13)
100.113.2	ACCCAAGCTTGGGATGCTGGGCTGGGAGGTGG (SEQ ID NO:14)
127.2.2	AGGACCGGTGGGATGCTGGGCTGGGAGGTGG (SEQ ID NO:24)
127.50.1	AGGACCGGTCAGGCTTCACCCCAGACCCAC (SEQ ID NO:29)
31.166.1	TGCGCCGGTGTACACAGGAAGTGA (SEQ ID NO:30)
32.32.1	GAGTTTGTGCCATCGGTCTAC (SEQ ID NO:31)
32.32.2	AATCAATCCTTAGTCCTCCTG (SEQ ID NO:32)
51.176	GCAGAAAAATCTTCCAAACACTCCC (SEQ ID NO:33)
99.120.1	ACGTACACCGGTCGTTACATAACTTAC (SEQ ID NO:34)
99.120.2	CTAGCAACCGGTCGGTTCACTAAACG (SEQ ID NO:35)

On page 119, please amend the paragraph containing line 18 as follows:

An ADP cassette is constructed using overlap PCR. The Y leader, an important sequence for correct expression of some late genes, is PCR amplified using primers:

5' GCCTTAATTAAAAGCAAACCTCACCTCCG...Ad2 28287bp (37.124.1) (SEQ ID NO:36); and

5' GTGGAACAAAAGGTGATTAAAAAATCCCAG...Ad2 28622bp (37.146.1) (SEQ ID NO:37).

The ADP coding region is PCR amplified using primers

5' CACCTTTTGTTCCACCGCTCTGCTTATTAC...Ad2 29195bp (37.124.3) (SEQ ID NO:38) and

5' GGCTTAATTAACTGTGAAAGGTGGGAGC...Ad2 29872bp (37.124.4) (SEQ ID NO:39).

On page 120, please amend the paragraph containing line 21 as follows:

CN248 (a construct that would allow introduction of an ADP cassette into a Ad that also contains a deletion/substitution in the E4 region) was made as follows. The E4 region was deleted by digesting CN108, a construct that contains right hand end Ad5 sequence from the unique EcoRI site in the E3 region, with AvrII and AflII. The only E4 ORF necessary for viral replication, ORF 6, was reintroduced by PCR amplifying the ORF with primers,

33.81.1 (Ad5 33096):

GCAGCTCACTTAAGTTCATGTCG (SEQ ID NO:40)

33.81.2 (Ad5 34084):

TCAGCCTAGGAAATATGACTACGTCCG (SEQ ID NO:41)

Beginning on page 122, please amend Table 6 as follows:

TABLE 6 IRES SEQUENCES

A 519 base pair IRES obtainable from encephelomycarditis virus (EMCV) (SEQ ID NO:42).

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1    GACGTCGACTAATTCCGGTTATTTTCCACCATATTGCCGTCTTTTGGCAA
       SalI
51   TGTGAGGGCCCGGAAACCTGGCCCTGTCTTCTTGACGAGCATTCCTAGGG
101  GTCTTTCCCCTCTCGCCAAAGGAATGCAAGGTCTGTTGAATGTCGTGAAG
151  GAAGCAGTTCCTCTGGAAGCTTCTTGAAGACAAACAACGTCTGTAGCGAC
201  CCTTTGCAGGCAGCGGAACCCCCCACCTGGCGACAGGTGCCTCTGCGGCC
251  AAAAGCCACGTGTATAAGATACACCTGCAAAGGCGGCACAACCCCAGTGC
301  CACGTTGTGAGTTGGATAGTTGTGGAAAGAGTCAAATGGCTCTCCTCAAG
351  CGTATTCAACAAGGGGCTGAAGGATGCCCAGAAGGTACCCCATTGTATGG
401  GATCTGATCTGGGGCCTCGGTGCACATGCTTTACATGTGTTTAGTCGAGG
451  TTAAAAAACGTCTAGGCCCCCCGAACCACGGGGACGTGGTTTTCCTTTGA
                SalI
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501 AAAACACGAT*GTCGAC*GTC

An IRES obtainable from vascular endothelial growth factor (VEGF) (SEQ ID NO:43).

1 ACGTA*GTCGAC*AGCGCAGAGGCTTGGGGCAGCCGAGCGGCAGCCAGGCCC
SalI

51 CGGCCCGGGCCTCGGTTCCAGAAGGGAGAGGAGCCCGCCAAGGCGCGCAA

101 GAGAGCGGGCTGCCTCGCAGTCCGAGCCGGAGAGGGAGCGCGAGCCGCGC

151 CGGCCCCGGACGGCCTCCGAAACCATG*GTCGAC*ACGTA
SalI

318

A 5'UTR region of HCV (SEQ ID NO:44).

1 GCCAGCCCCCTGATGGGGGCGACACTCCGCCATGAATCACTCCCCTGTGAGGAACTACTG

61 TCTTCACGCAGAAAGCGTCTAGCCATGGCGTTAGTATGAGTGTCGTGCAGCCTCCAGGAC

121 CCCCCCTCCCGGGAGAGCCATAGTGGTCTGCGGAACCGGTGAGTACACCGGAATTGCCAG

181 GACGACCGGGTCCTTTCTTGGATTAACCCGCTCAATGCCTGGAGATTTGGGCGTGCCCCC

241 GCAAGACTGCTAGCCGAGTAGTGTTGGGTCGCGAAAGGCCTTGTGGTACTGCCTGATAGG

301 GTGCTTGCGAGTGCCCCGGGAGGTCTCGTAGACCGTGCACC (341)

A 5'UTR region of BiP (SEQ ID NO:45)

1 CCCGGGGTCACTCCTGCTGGACCTACTCCGACCCCCTAGGCCGGGAGTGAAGGCGGGACT

61 TGTGCGGTTACCAGCGGAAATGCCTCGGGGTCAGAAGTCGCAGGAGAGATAGACAGCTGC

121 TGAACCAATGGGACCAGCGGATGGGGCGGATGTTATCTACCATTGGTGAACGTTAGAAAC

181 GAATAGCAGCCAATGAATCAGCTGGGGGGGCGGAGCAGTGACGTTTATTGCGGAGGGGGC

241 CGCTTCGAATCGGCGGCGGCCAGCTTGGTGGCCTGGGCCAATGAACGGCCTCCAACGAGC

301 AGGGCCTTCACCAATCGGCGGCCTCCACGACGGGGCTGGGGGAGGGTATATAAGCCGAGT

361 AGGCGACGGTGAGGTCGACGCCGGCCAAGACAGCACAGACAGATTGACCTATTGGGGTGT

421 TTCGCGAGTGTGAGAGGGAAGCGCCGCGGCCTGTATTTCTAGACCTGCCCTTCGCCTGGT

481 TCGTGGCGCCTTGTGACCCCGGGCCCCTGCCGCCTGCAAGTCGAAATTGCGCTGTGCTCC

541 TGTGCTACGGCCTGTGGCTGGACTGCCTGCTGCTGCCCAACTGGCTGGCAAGATG (595)

A 5'UTR of PDGF (SEQ ID NO:46).

```
1       GTTTGCACCTCTCCCTGCCCGGGTGCTCGAGCTGCCGTTGCAAAGCCAACTTTGGAAAAA

61      GTTTTTTGGGGGAGACTTGGGCCTTGAGGTGCCCAGCTCCGCGCTTTCCGATTTTGGGGG

121   CTTTCCAGAAAATGTTGCAAAAAAGCTAAGCCGGCGGGCAGAGGAAAACGCCTGTAGCCG

181   GCGAGTGAAGACGAACCATCGACTGCCGTGTTCCTTTTCCTCTTGGAGGTTGGAGTCCCC

241   TGGGCGCCCCCACACCCCTAGACGCCTCGGCTGGTTCGCGACGCAGCCCCCCGGCCGTGG

301   ATGCTGCACTCGGGCTCGGGATCCGCCCAGGTAGCCGGCCTCGGACCCAGGTCCTGCGCC

361   CAGGTCCTCCCCTGCCCCCCAGCGACGGAGCCGGGGCCGGGGGCGGCGGCGCCGGGGGCA

421   TGCGGGTGAGCCGCGGCTGCAGAGGCCTGAGCGCCTGATCGCCGCGGACCTGAGCCGAGC

481   CCACCCCCCTCCCCAGCCCCCCACCCTGGCCGCGGGGGCGGCGCGCTCGATCTACGCGTC

541   CGGGGCCCCGCGGGGCCGGGCCCGGAGTCGGCATG (575)
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B18 cont'd